Patent

Attorney's Docket No. 1017753-000150

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP AF**
Michel Koehl et al.	Group Art Unit: **1648**
Application No.: 09/914,036	Examiner: STACY BROWN CHEN
Filing Date: December 10, 2001	Confirmation No.: 8634
Title: METHOD FOR OBTAINING A PURIFIED VIRAL PREPARATION	

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s). (Note: no more than five pages may be provided.)

Respectfully submitted,

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Date: March 14, 2007

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Request for Pre-Appeal Brief Review Conference

Prior to filing an Appeal Brief, Applicants request review of the single remaining rejection in the captioned application prior to the filing of an Appeal Brief in accordance with the Pre-Appeal Brief Conference Pilot Program described in the Official Gazette on 12 July 2005.

In the final Office Action, mailed September 14, 2006, the Office has maintained a rejection of pending claims 19-34 and 36-38 under 35 U.S.C. § 103(a) for allegedly being unpatentable over Shabram et al., WO 96/27677 A2 ("Shabram"), in view of Berg, WO 98/33572 A1 ("Berg"), Bondoc et al., *J. Indust. Micro. & Biotech.*, 20:317-322, 1998 ("Bondoc"), and Georgiou et al., U.S. Patent Number 6,027,888 ("Georgiou").

The rejection is improper, because the prior art fails to establish a proper prima facie case of obviousness. Furthermore, secondary indicia of non-obviousness, specifically the substantial improvement in yield of infectious particles obtained using the claimed methods compared to the methods disclosed in the prior art have not been given sufficient consideration.

To establish a prima facie case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. M.P.E.P. § 2143; *In re Rouffet*, 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998) ("[T]the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.").

The presently claimed invention is directed to a method comprising two steps for purifying infectious adenoviral particles from a crude viral preparation. The presently claimed methods utilize a fluidized bed chromatography step wherein the particles of adsorbent comprise an agarose matrix with a central core comprising quartz, and dextran chains covalently coupled

to the agarose matrix, on which are attached positively charged groups (such as Streamline XL or QXL), and a gel filtration chromatography step that is carried out on a support comprising an alkyl dextran and methylene bisacrylamide matrix or an ethylene glycol and methacrylate matrix.

Shabram is also directed to purifying recombinant adenovirus particles by a method comprising two steps. However, neither of the steps taught by Shabram is the same as a step of the present invention. The prior art provided no guidance related to the problem solved by the present invention that would have lead a person of ordinary to select the particular elements of the invention for combination in the manner claimed.

In contrast to the specific and distinct features of the fluidized bed chromatography step of the presently claimed combination, Shabram generally teaches an anion exchange chromatography step, providing only specific examples using conventional DEAE column chromatography. Shabram does not teach or suggest particles of adsorbent comprising an agarose matrix and a central core comprising quartz, and dextran chains covalently coupled to said agarose matrix, on which are attached positively charged groups.

Every embodiment demonstrated by Shabram involves conventional column chromatography, not fluidized bed chromatography as required in the first chromatography step recited in the present claims. The only mention of fluidized bed chromatography by Shabram is in a single broadly general statement: "The resins can be used in a traditional (gravity) column chromatography or high pressure liquid chromatography apparatus using radial or axial flow, fluidized bed columns, or in a slurry (batch) method." Shabram at col. 5, lines 26-29. This broad listing of known chromatography techniques provides no motivation to choose fluidized bed chromatography from among all possible chromatographic techniques. At best, Shabram's

statement is an invitation to experiment, not a suggestion to practice the particular step of the present invention in the manner claimed.

The Office has asserted that this "does not mean that one of ordinary skill would not have considered fluidized bed chromatography to be an alternative method." OFFICE ACTION MAILED SEPTEMBER 14, 2006 AT 5. However, that is not a sufficient finding. A finding as to the specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with no knowledge of the present invention to make the combination in the manner claimed is required to make out a proper *prima facie* case of obviousness. *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1318 (Fed. Cir. 2000).

The failure of Shabram to appreciate the benefits of fluidized bed chromatography demonstrates that it could not have been obvious to substitute fluidized bed chromatography for the traditional methods that Shabram demonstrated. The present inventors found that fluidized bed chromatography can provide an 80% yield of infectious viral particles compared to at most 60% yield achieved by packed bed chromatography such as Shabram demonstrated. *See,* Specification at 26-27. Shabram reported a 67% yield of total particles using conventional anion exchange chromatography. Shabram at col. 13, TABLE 1.

The Office has cited Berg for its general teaching of fluidized bed chromatography using adsorbent comprising an agarose matrix with a central core comprising quartz, and dextran chains covalently coupled to the agarose matrix, on which are attached positively charged groups. However, the Office has acknowledged that Berg, taken alone, would not motivate one of ordinary skill to use fluidized bed chromatography for purifying adenoviruses. Office Action mailed September 14, 2006 at 6. This is because Berg is not directed to purification of large and complex adenoviral particles, but rather the purification of macromolecules and water soluble

polymers. Berg specifically teaches that "the process is normally limited to the adsorption/separation of compounds that have a molecular weight below 1,000,000." Berg at 12, lines 14-16. Adenoviral particles are much more complex structures comprising many individual proteins encapsulating a viral genome and are more than two orders of magnitude larger than the limit of fluidized bed chromatography taught by Berg. Therefore, one would not have had any specific motivation to substitute the materials described by Berg for the materials described by Shabram or to utilize a fluidized bed chromatography step in Shabram's method.

Given Shabram's failure to appreciate the superior yield of infectious viral particles provided by fluidized bed chromatography and the Office's acknowledgement that Berg would not have motivated one of ordinary skill to use fluidized bed chromatography for purifying adenoviruses, Applicants submit that it could not have been obvious to modify the anion exchange step of Shabram to utilize the particular technique and materials required by the presently claimed method.

Furthermore, in contrast to the gel filtration chromatography step of the presently claimed combination, Shabram teaches a second step using immobilized metal affinity chromatography (IMAC) and provides an example where the metal is zinc. See, Shabram at col. 3, lines 58-67, and columns 10-12. Shabram also specifically teaches that hydrophobic interaction chromatography (HIC) can be substituted for the IMAC step. Shabram at col. 6, lines 32-33. Shabram does not teach or suggest a gel filtration chromatography step that is carried out on a support comprising an alkyl dextran and methylene bisacrylamide matrix or an ethylene glycol and methacrylate matrix.

Bondoc is cited for teaching gel filtration of adenovirus particles. However, Bondoc fails to teach or suggest the chromatographic support utilized in the presently claimed methods. The

Office has alleged that "[l]ooking to Georgiou, for teaching regarding gel filtration would lead one to use any number of materials, including a dextran/methylene bisacrylamide matrix (col. 38, lines 44-65)" OFFICE ACTION MAILED SEPTEMBER 14, 2006.

However, Georgiou would not have suggested the gel filtration step of the presently claimed invention for use in the presently claimed combination. Firstly, a person of ordinary skill in the art would not have looked to Georgiou for teaching regarding purification of adenovirus particles, because Georgiou is directed to solving the unrelated problem of producing disulfide containing eukaryotic proteins in prokaryotes. Purifying adenovirus particles is a different problem requiring different considerations. Secondly, as the Office acknowledges, the general teaching of Georgiou would lead one to use any number of materials. However, that is not sufficient to make out a prima facie case of obviousness. A specific understanding or principle within the knowledge of a skilled artisan that would have motivated one to make the combination in the manner claimed is required to make out a proper *prima facie* case of obviousness. *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1318 (Fed. Cir. 2000).

To arrive at the claimed methods, a person of ordinary skill in the art would have to modify or substitute both of the steps taught by Shabram, choosing from among a myriad of possible combinations of alternative steps and various of materials without any particular guidance related to the problem solved by the present invention. It is not enough that one of skill in the art would be aware of the individual elements comprising the present invention. *See, In re Rouffet*, 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998)("The examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.")(emphasis added)).